

Incidence of Bacterial and Fungal Secondary Infections in COVID-19 Patients Admitted to the ICU

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Purpose: Secondary infections have been observed among coronavirus disease 2019 (COVID-19) patients, especially in the intensive care unit (ICU) setting, which is associated with worse clinical outcomes. The current study aimed to investigate the incidence, common pathogens, and outcome of bacterial and fungal secondary infections among ICU patients with COVID-19.

Methods: A retrospective chart review of all patients admitted to the ICU at King Fahd Hospital of the University in Saudi Arabia. All adult patients aged ≥ 18 admitted in the ICU for ≥ 48 hours with positive COVID-19 reverse transcription-polymerase chain reaction test during the period between March 2020 till September 2021 were included.

Results: Out of 314 critically ill patients, 133 (42.4%) developed secondary infections. The incidence of secondary bacterial infection was 32.5% with *Pseudomonas aeruginosa* (n = 34), *Acinetobacter baumannii* (n = 33), and *Klebsiella pneumoniae* (n = 17) being the predominant pathogens, while secondary fungal infection was 25.2% mainly caused by *Candida albicans* (n = 43). Invasive mechanical ventilation was significantly associated with the development of secondary bacterial infections (odds ratio [OR] = 17.702, 95% confidence interval [CI] 7.842–39.961, $p < 0.001$) and secondary fungal infections (OR = 12.914, 95% CI 5.406–30.849, $p < 0.001$). Mortality among patients with secondary infections was 69.2% (n = 92). Secondary infections were associated with longer hospital and ICU stays with a median of 25 days (interquartile range [IQR] 17–42) and 19 days (IQR 13–32), respectively.

Conclusion: Bacterial and fungal secondary infections are common among COVID-19 patients admitted to the ICU with a predominance of gram-negative bacteria and *Candida* species. The development of secondary infections was significantly associated with invasive mechanical ventilation. Poor clinical outcomes have been observed, demonstrated with a prolonged hospital and ICU stays and higher mortality.

Keywords: COVID-19, intensive care unit, secondary infection, bacterial, fungal

Introduction

The novel Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has posed a significant global health challenge.¹ On March 11th, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic.² The clinical manifestation varies from asymptomatic carriers to critical disease necessitating admission to the Intensive Care Unit (ICU).^{1,3} Around 5% of COVID-19 patients and 20% of those hospitalized require ICU admission, of which the case fatality rate reaches up to 40%.³ The newly emerging SARS-CoV-2 resulted in approximately six million deaths worldwide⁴ and 9001 deaths in Saudi Arabia.⁵

In line with previous viral pandemics, co-infections and secondary infections have been reported to occur in COVID-19 patients. In a recently published systematic review and meta-analysis,⁶ the pooled prevalence of infections secondary to SARS-CoV-2 was 24%, with the highest observed in ICU patients (41%). Co-infections, on the other hand, had a pooled prevalence of 19%, with the highest prevalence reported among non-ICU patients (29%) compared to only ICU

co-infected patients (16%). Bacterial pathogens were the organisms most commonly implicated in secondary infections (20%), the most frequently identified of which were *Acinetobacter* species, *Pseudomonas*, and *Escherichia coli*. Fungal secondary infections, notably by *Candida* species (*Candida* spp), were also reported in the literature (8%). On the other hand, the least frequently observed culprits were viral secondary infections (4%), the most common of which were rhinoviruses.⁶

It has been suggested that SARS-CoV-2 infected patients are prone to develop secondary infection potentially due to their immunosuppressed condition induced by the primary infection and medications.⁷ There is insufficient data concerning possible factors associated with acquiring secondary infections among COVID-19 patients. Nevertheless, it has been reported that secondary infections were mainly related to ICU admission, mechanical ventilation, and catheterization.⁸ In addition, the use of corticosteroids and broad-spectrum antibiotics in severely ill COVID-19 patients favors the development of opportunistic infections.⁹ Existing literature has documented poor clinical outcomes among COVID-19 patients suffering from secondary infection, including higher mortality and longer stay in the hospital.^{6,10} This study aims to identify the incidence of bacterial and fungal secondary infections among COVID-19 patients admitted to the ICU at King Fahd Hospital of the University, Khobar, Saudi Arabia.

Methods

Patients and Settings

The present retrospective study assessed all patients admitted to the ICU at King Fahd Hospital of the University, Khobar, Saudi Arabia, during the period of March 2020 to September 2021. All adult patients aged ≥ 18 years admitted to the ICU for ≥ 48 hours with a positive COVID-19 Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) test were included. Patients who stayed in the ICU for < 48 hours and those who had an incidental finding of SARS-CoV-2 were excluded.

Data Collection

Data of eligible subjects were extracted from their electronic medical records. Extracted data included patients' characteristics pertaining to demographics (gender, age, smoking, and Body Mass Index [BMI]), date of first positive COVID-19 PCR test, co-morbidities (obesity, diabetes mellitus, hypertension, chronic pulmonary diseases, cardiovascular diseases, chronic kidney diseases, and immunosuppressed status), mechanical ventilation (invasive mechanical ventilation, and duration of invasive mechanical ventilation), medical management (antibiotics, antifungals, antivirals, corticosteroids, and immunomodulatory agents [Tocilizumab]), and invasive management (central venous catheter, vasopressors, Continuous Renal Replacement Therapy [CRRT], and Extracorporeal Membrane Oxygenation [ECMO]). The management, including the dosing of corticosteroids, was followed as per the Saudi ministry of health COVID-19 guidelines.¹¹

Definitions

A secondary infection implies the emergence of bacterial or fungal infections during the course of SARS-CoV-2 illness following 48 hours from hospital admission, while identification of those infections during the first 48 hours from admission is consistent with a co-infection.

SARS-CoV-2 screening at admission was carried out with Nasopharyngeal swabs using viral transport media (Viracell, Granada, Spain) which were delivered to the laboratory on ice packs for rapid processing. Identification of SARS-CoV-2 was through RT-PCR test via the Xpert[®] Xpress SARS-CoV-2 (Cepheid, Sunnyvale, USA), detecting N2 and E genes in SARS-CoV-2 as per the manufacturer's recommendations along with using negative and positive controls. Biosafety cabinet class-II type-B was followed for all samples processed to reduce the occupational risk. All samples were processed in biosafety Level II laboratory since no viral propagation nor aerosol generating procedure was carried out.

Microbiological identification of bacteria and fungi was through growth of cultures recovered from blood, respiratory system (trans-tracheal aspirate, broncho-alveolar lavage, and sputum), and other specimens (urine, wound, abscess,

vaginal, ear, and pleural fluid) during patients' ICU stay. The aforementioned specimens were grown on the corresponding routine bacteriological media using chocolate agar, Columbia Blood agar, MacConkey agar plates (SPML, Riyadh, Saudi Arabia), and were incubated at 35 °C anaerobically and aerobically for 24 to 48 hours. Identification of significant growth within cultures is done through VITEK[®] MS (bioMérieux Inc., Durham, North Carolina, USA), an automated mass spectrometry microbial identification system based on matrix-assisted laser desorption ionization time-of-flight (MALDI- TOF) technology. *Staphylococcus epidermidis* positive cultures, due to possible contamination, were excluded.

Outcomes

The primary outcome of this study was the incidence of bacterial and fungal secondary infections among patients with COVID-19 admitted to the ICU. The secondary outcome is identifying the common pathogens, factors associated with secondary infections, mortality, and length of ICU and hospital stays among patients who developed secondary infections.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 26.0 (IBM, New York, USA). Normality of continuous data was assessed, and parametric and non-parametric data are presented as either mean and Standard Deviation (SD) or as median and Interquartile Range (IQR), respectively. Student's *t*-test and Mann-Whitney *U*-test were used to compare the means of patients who acquired a secondary bacterial infection to those with no secondary bacterial infection and patients with a secondary fungal infection to those with no secondary fungal infection. Categorical binomial variables are presented as frequencies and percentages and analyzed by either Pearson's Chi-square test or Fisher's exact test. Binary logistic regression analyses were carried out to evaluate the association between (a) selected variables (gender, age, BMI, co-morbidities, and ICU management) and the odds of acquiring bacterial or fungal secondary infections and (b) acquiring bacterial or fungal secondary infections and the odds of mortality. The aforementioned are presented as Odds Ratio (OR) and Confidence Interval (CI). The date in which bacterial or fungal cultures first turned positive for each patient was recorded, and the pathogens implicated in all secondary infections are further described. The CI was set at 95% corresponding to a *p* value of 0.05, values below of which were considered significant.

Ethical Approval

Ethical approval for this study was granted by the Institutional Review Board at Imam Abdulrahman bin Faisal University (IRB-UGS-2021-01-388), who waived the need for written consent due to the retrospective design of the study. The data was collected taking into consideration patients' confidentiality in accordance with the Declaration of Helsinki.

Results

During the study period, 403 COVID-19 positive patients were admitted to the ICU. Eighty-nine patients were excluded and a total of 314 patients met the inclusion criteria and were enrolled in the present study. Of these, 204 (65%) patients were male. The mean age was 57.68 years (SD= ±14.80, n=314), with a median BMI of 30.48 kg/m² (IQR 26.76–35.16, n= 246). Twenty-six (8.3%) patients were smokers. The vast majority of patients (85.7%) had underlying comorbidities. The predominant comorbid conditions identified were diabetes mellitus (56%), hypertension (51.9%), and obesity (44.9%).

Throughout the course of ICU admission, all patients have received antibiotics, wherein corticosteroids and antivirals were prescribed to 293 (93.3%) and 256 (81.5%) patients, respectively. Tocilizumab was given to 103 (32.8%) patients. Similarly, 104 (33.1%) patients received antifungals. During their stay in the ICU, 196 (62.4%) patients underwent various invasive interventions. One hundred and eighty-seven (59.6%) patients were on invasive mechanical ventilation. Central venous catheter was inserted in 137 (43.6%) patients, while vasopressors were required by 117 (37.3%) patients. CRRT was initiated in 95 (30.3%) patients. Only 3 (1%) patients were supported by ECMO. Table 1 summarizes the demographic and clinical characteristics of the included patients.

Table 1 Demographic and Clinical Characteristics of 314 Patients with COVID-19 Admitted to the ICU for ≥ 48 Hours

Characteristic	No Secondary Infection (n = 181)	Secondary Bacterial Infection (n = 102)		Secondary Fungal Infection (n = 79)	
		Value	p ^a	Value	p ^b
Male	124 (68.5)	66 (64.7)	0.946	40 (50.6)	0.002
Age (years)	56 (± 15)	59.99 (± 13.19)	0.054	61 (± 16)	0.009
Smoking	16 (8.8)	9 (8.8)	0.809	4 (5.1)	0.23
BMI (kg/m ²)	31.1 (27.49–35.16)	29.6 (25.5–34.60)	0.048	31 (26.8–36.5)	0.519
Obesity	82 (52.9)	41 (43.6)	0.090	43 (57.3)	0.18
Comorbidities					
Diabetes	98 (54.1)	57 (55.9)	0.967	50 (63.3)	0.134
Hypertension	86 (47.5)	60 (58.8)	0.089	51 (64.6)	0.009
Cardiovascular disease	30 (16.6)	13 (12.7)	0.147	23 (29.1)	0.001
Chronic renal disease	23 (12.7)	19 (18.6)	0.306	19 (24.1)	0.017
Chronic lung disease	15 (8.3)	12 (11.8)	0.355	11 (13.9)	0.127
Immunosuppression	6 (3.3)	7 (6.9)	0.093	5 (6.3)	0.259
Medical management					
Antibiotics	181 (100)	102 (100)	Undefined ^c	79 (100)	Undefined ^c
Antifungals	25 (13.8)	59 (57.8)	<0.001	57 (72.2)	<0.001
Antivirals	154 (85.1)	81 (79.4)	0.503	60 (75.9)	0.14
Corticosteroids	162 (89.5)	101 (99)	0.005	77 (97.5)	0.087
Tocilizumab	62 (34.3)	32 (31.4)	0.708	24 (30.4)	0.596
Invasive management					
Invasive mechanical ventilation	65 (35.9)	95 (93.1)	<0.001	73 (92.4)	<0.001
Duration of invasive mechanical ventilation (days)	5 (2–10)	13 (8–24)	<0.001	14 (7–24)	<0.001
Central venous catheter	44 (24.3)	71 (69.6)	<0.001	60 (75.90)	<0.001
Vasopressors	35 (19.3)	62 (60.8)	<0.001	53 (67.1)	<0.001
CRRT	30 (16.6)	47 (46.1)	<0.001	42 (53.2)	<0.001
ECMO	0 (0)	2 (2)	0.204	2 (2.5)	0.157
Mortality	53 (29.3)	67 (65.7)	<0.001	57 (72.2)	<0.001
Length of hospital Stay (days)	14 (9–21)	31 (19–46)	<0.001	28 (19–42)	<0.001
Length of ICU stay (days)	7 (5–11)	21 (13–37)	<0.001	21 (15–35)	<0.001

Notes: Data are presented as frequencies (%), median (interquartile range), or mean (\pm standard deviation). Forty-nine patients developed a secondary bacterial and fungal infection. Numbers in bold indicate significant p-values. ^aComparison of patients with secondary bacterial infection versus no secondary bacterial infection. ^bComparison of patients with secondary fungal infection versus no secondary fungal infection. ^cUndefined because p value could not be calculated with a row value of zero.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; BMI, body mass index; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Incidence of Secondary Infection (Primary Outcome)

A total of 133 (42.4%) patients developed secondary infections, of which 56.4% were bacterial and 43.6% were fungal. Among the study sample, 48 (15.3%) patients had both bacterial and fungal secondary infections during their ICU stay. Figure 1 shows the incidence of different bacterial and fungal secondary infections. Respiratory system infection was the most common secondary infection with an incidence of 32.5% (n=102) followed by bloodstream infection (n=64, 20.4%). The median duration of developing a secondary infection from the day of admission was 11 days (IQR 6.5–16.5). A minority of patients had a positive culture within 48 hours of admission, implying a co-infection, which represents 12.1% of all patients (n=38).

Most Common Pathogens

Secondary bacterial infection was identified in 102 (32.5%) patients. The most frequently isolated bacterial pathogens were *Pseudomonas aeruginosa* (n=34), *Acinetobacter baumannii* (n=33), and *Klebsiella pneumoniae* (n=17). Among patients with secondary bacterial infection, 53 (52%) patients had bacteremia. The most prevalent pathogens identified

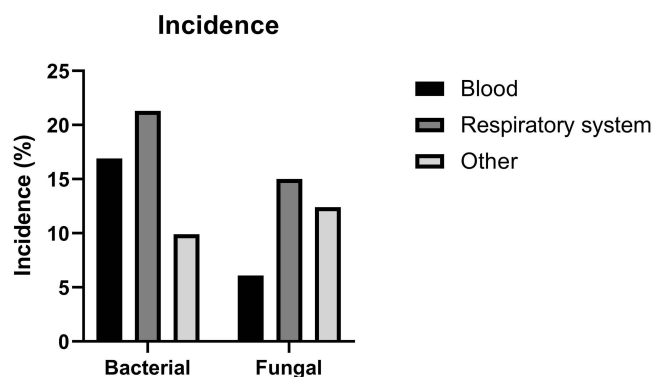


Figure 1 Incidence of secondary bacterial and fungal infections in 314 patients with COVID-19 admitted in the ICU.

were *Acinetobacter baumannii* (n=11), *Staphylococcus capitis* (n=7), and *Staphylococcus haemolyticus* (n=7). Respiratory bacterial cultures were positive in 67 (65.7%) patients. The predominant respiratory pathogens were *Acinetobacter baumannii* (n=29), *Pseudomonas aeruginosa* (n=28), and *Klebsiella pneumoniae* (n=10). Secondary fungal infection was identified in 79 (25.2%) patients with *Candida Albicans* (n=43), *Candida tropicalis* (n=24), and *Candida parapsilosis* (n=8) being the most common. All documented bacterial and fungal secondary infections are presented in Tables 2 and 3, respectively.

Factors Associated with Secondary Infection

Out of 133 patients who developed secondary infections, 60.2% were male. Secondary fungal infections were found in 35.5% of females (n=39, $p = 0.002$). Fungal secondary infections were significantly associated with advanced age (OR = 1.024, 95% CI 1.006–1.042, $p = 0.01$). Multiple comorbidities were significantly associated with developing a secondary

Table 2 Detailed Epidemiology of Documented Bacterial Infections Secondary to COVID-19 in 102 Patients Admitted in the ICU

Pathogen	Total (n = 214)	Blood (n = 72)	Respiratory System (n = 94)	Other (n = 48)
Bacterial secondary infections				
<i>Acinetobacter baumannii</i>	45	11	29	5
<i>Pseudomonas aeruginosa</i>	41	5	28	8
<i>Klebsiella pneumoniae</i>	22	5	10	7
<i>Enterococcus faecalis</i>	16	6	2	8
<i>Escherichia coli</i>	13	2	3	8
<i>Stenotrophomonas maltophilia</i>	10	1	9	–
<i>Enterococcus faecium</i>	9	4	–	5
<i>Staphylococcus haemolyticus</i>	8	7	1	–
<i>Staphylococcus capitis</i>	7	7	–	–
<i>Serratia marcescens</i>	6	2	2	2
<i>Staphylococcus hominis</i>	6	6	–	–
<i>Staphylococcus aureus</i>	5	1	3	1
<i>Enterobacter cloacae</i> complex	3	2	1	–
<i>Morganella morganii</i>	3	1	–	2
<i>Acinetobacter pittii</i>	2	–	2	–
Coagulase –ve staphylococcus	2	1	1	–
<i>Enterobacter aerogenes</i>	2	1	1	–
<i>Ralstonia mannitolilytica</i>	2	2	–	–

(Continued)

Table 2 (Continued).

Pathogen	Total (n = 214)	Blood (n = 72)	Respiratory System (n = 94)	Other (n = 48)
<i>Bacteroides</i> species	1	1	–	–
<i>Burkholderia cepacia</i>	1	1	–	–
<i>Citrobacter freundii</i>	1	1	–	–
<i>Dermabacter hominis</i>	1	1	–	–
<i>Enterobacter asburiae</i>	1	–	–	1
<i>Gardnerella vaginalis</i>	1	–	–	1
<i>Granulicatella adiacens</i>	1	1	–	–
<i>Lactobacillus</i> species	1	1	–	–
<i>Pseudomonas putida</i>	1	–	1	–
<i>Ralstonia</i> species	1	–	1	–
<i>Streptococcus mitis</i>	1	1	–	–
<i>Streptococcus parasanguinis</i>	1	1	–	–

Note: Forty-nine patients developed a secondary bacterial and fungal infection.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Table 3 Detailed Epidemiology of Documented Fungal Infections Secondary to COVID-19 in 79 Patients Admitted in the ICU

Pathogen	Total (n = 119)	Blood (n = 20)	Respiratory System (n = 58)	Other (n = 41)
Fungal secondary infections				
<i>Candida albicans</i>	53	9	23	21
<i>Candida tropicalis</i>	31	5	15	11
<i>Candida parapsilosis</i>	9	3	5	1
<i>Candida dubliniensis</i>	6	–	5	1
<i>Aspergillus</i> species	4	–	4	–
<i>Candida krusei</i>	4	1	2	1
<i>Candida glabrata</i>	3	–	–	3
<i>Candida auris</i>	2	1	–	1
<i>Candida</i> species	2	–	2	–
<i>Trichosporon asahii</i>	2	–	–	2
<i>Candida guilliermondii</i>	1	–	1	–
<i>Candida lusitanae</i>	1	–	1	–
<i>Candida orthopsilosis</i>	1	1	–	–

Note: Forty-nine patients developed a secondary bacterial and fungal infection.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

fungal infection including hypertension, cardiovascular disease, and chronic renal disease ([OR = 2.0, 95% CI 1.181–3.389, $p = 0.009$], [OR = 2.703, 95% CI 1.461–5.0, $p = 0.001$], and [OR = 2.164, 95% CI 1.138–4.115, $p = 0.017$], respectively). On the contrary, smoking, obesity, diabetes, chronic lung disease, and immunosuppression were not significantly associated with developing a secondary bacterial nor fungal infection (Table 4).

A significantly higher use of corticosteroids was found among patients with secondary bacterial infection (OR = 10.521, 95% CI 1.392–79.529, $p = 0.023$). In contrast, the development of fungal infection was not significantly associated with corticosteroids (OR = 3.387, 95% CI 0.771–14.878, $p = 0.087$). As shown in Table 4, the association between tocilizumab or antiviral agents and the development of secondary infections was found to be statistically nonsignificant.

Secondary bacterial and fungal infections were significantly associated with invasive mechanical ventilation ([OR = 17.702, 95% CI 7.842–39.961, $p < 0.001$], and [OR = 12.914, 95% CI 5.406–30.849, $p < 0.001$], respectively).

A significantly longer duration of invasive mechanical ventilation was observed among patients suffering from secondary bacterial and fungal infections ([OR = 1.104, 95% CI 1.061–1.149, $p < 0.001$], and [OR = 1.047, 95% CI 1.016–1.079, $p = 0.003$], respectively). Almost all patients ($n=100$, 98%) with a secondary respiratory system infection were mechanically ventilated, representing 53.5% of those requiring invasive mechanical ventilation support. The median duration for growing a positive bacterial culture after the initiation of invasive mechanical ventilation was 7 days (IQR 3–11), as opposed to 3 days (IQR 1–8.5) for isolating a fungal pathogen. Moreover, secondary infected patients with bacterial and fungal pathogens were found to be subjected to more invasive interventions including central venous catheterization, CRRT, and vasopressors, as presented in Table 4.

Outcome of Secondary Infection

Mortality among patients with bacterial and fungal infections secondary to SARS-CoV-2 was 69.2% ($n=92$, $p < 0.001$). Sixty-seven (65.7%) deaths were observed among patients who acquired a secondary bacterial infection compared to 57 (72.2%) deaths for fungal. Increased odds of mortality were observed among those who developed secondary infection (OR= 5.419, 95% CI 3.327–8.826, $p < 0.001$), with fungal infection having higher odds (OR= 4.328, 95% CI 2.476–7.565, $p < 0.001$) as compared to bacterial (OR= 3.289, 95% CI 2.005–5.395, $p < 0.001$).

Table 4 Binary Logistic Regression Analyses Investigating the Association Between Variables of Interest and the Odds of Acquiring Bacterial and Fungal Secondary Infections in Patients with COVID-19 Admitted in the ICU

Characteristic	Secondary Bacterial Infection (n = 102)		Secondary Fungal Infection (n = 79)	
	OR (95% CI)	p^a	OR (95% CI)	p^b
Male	0.983 (0.599–1.612)	0.946	0.444 (0.264–0.748)	0.002
Age (years)	1.016 (1.000–1.033)	0.056	1.024 (1.006–1.042)	0.01
Smoking	1.110 (0.477–2.584)	0.809	0.516 (0.172–1.547)	0.23
BMI (kg/m ²)	0.963 (0.927–1.000)	0.051	1.004 (0.969–1.041)	0.822
Comorbidities				
Obesity	0.650 (0.394–1.072)	0.091	1.44 (0.844–2.456)	0.18
Diabetes	0.990 (0.615–1.593)	0.967	1.492 (0.883–2.52)	0.134
Hypertension	1.512 (0.938–2.437)	0.090	2 (1.181–3.389)	0.009
Cardiovascular disease	0.609 (0.310–1.196)	0.150	2.703 (1.461–5)	0.001
Chronic renal disease	1.389 (0.739–2.609)	0.307	2.164 (1.138–4.115)	0.017
Chronic lung disease	1.437 (0.664–3.110)	0.357	1.839 (0.834–4.056)	0.127
Immunosuppression	2.530 (0.828–7.732)	0.103	1.917 (0.608–6.041)	0.259
Medical management				
Antibiotics	Undefined ^c		Undefined ^c	
Antifungals	5.092 (3.050–8.502)	<0.001	10.364 (5.764–18.634)	<0.001
Antivirals	0.816 (0.449–1.481)	0.503	0.628 (0.338–1.168)	0.14
Corticosteroids	10.521 (1.392–79.529)	0.023	3.387 (0.771–14.878)	0.087
Tocilizumab	0.908 (0.547–1.506)	0.708	0.862 (0.497–1.494)	0.596
Invasive management				
Invasive mechanical ventilation	17.702 (7.842–39.961)	<0.001	12.914 (5.406–30.849)	<0.001
Duration of invasive mechanical ventilation (days)	1.104 (1.061–1.149)	<0.001	1.047 (1.016–1.079)	0.003
Central Venous Catheter	5.066 (3.035–8.457)	<0.001	6.48 (3.616–11.613)	<0.001
Vasopressors	4.425 (2.677–7.312)	<0.001	5.447 (3.142–9.442)	<0.001
CRRT	2.920 (1.762–4.838)	<0.001	3.898 (2.277–6.672)	<0.001
ECMO	4.220 (0.378–47.090)	0.242	6.078 (0.544–67.958)	0.157

Notes: Forty-nine patients developed a secondary bacterial and fungal infection. Numbers in bold indicate significant p -values. ^aComparison of patients with secondary bacterial infection versus no secondary bacterial infection. ^bComparison of patients with secondary fungal infection versus no secondary fungal infection. ^cUndefined because odds ratio (OR) could not be calculated with a zero cell.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; BMI, body mass index; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

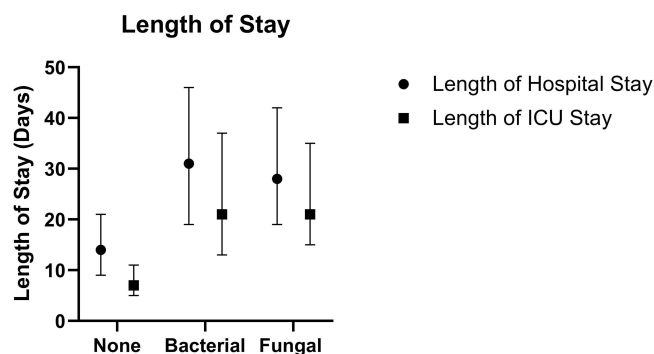


Figure 2 Length of hospital and ICU stays in 314 patients with COVID-19 admitted in the ICU with no secondary infections, secondary bacterial infections, and secondary fungal infections.

Patients who acquired secondary infections had a significantly prolonged stay in the ICU with a median of 19 days (IQR 13–32) in contrast to 7 days (IQR 5–11) in those who did not ($p < 0.001$). A significantly longer hospital stay was observed among patients who developed a secondary infection with a median of 25 days (IQR 17–42) as opposed to 14 days (IQR 9–21) in those without a secondary infection ($p < 0.001$). Patients who acquired bacterial and fungal secondary infections, in particular, had a longer ICU stay, both of which having a median of 21 days ([IQR 13–37, $p < 0.001$], and [IQR 15–35, $p < 0.001$], respectively). Consistently, duration of hospital stay was significantly prolonged among patients with a secondary bacterial infection with a median of 31 days (IQR 19–46, $p < 0.001$). Similarly, patients with a secondary fungal infection had a median of 28 days (IQR 19–42, $p < 0.001$), as shown in Figure 2.

Discussion

The present study investigated the incidence of bacterial and fungal secondary infections among ICU patients with COVID-19 and assessed their clinical outcome. We report a high incidence of secondary infection of 42.4% with a predominance of gram-negative bacteria and *Candida* spp. Our results are congruent with recent cohort studies conducted in Brazil⁹ and Spain¹² which reported an incidence of 41.8% and 40.7%, respectively. In China, a higher incidence of secondary infections (57.89%) was identified among critically ill and severe critically ill patients diagnosed with COVID-19.¹³ Nevertheless, a relatively lower incidence was observed in England¹⁴ and North India¹⁵ (30.3% and 22.6%, respectively). These variations in the literature could be attributed to the different sample size across studies and the disparity between populations. The median duration between admission to developing a secondary infection was 11 days (IQR 6.5–16.5), in line with the findings of Baskaran et al who described a period of 9 days (IQR 6–14).¹⁴

The current study found that 32.5% of patients acquired a secondary bacterial infection, while 25.2% had a secondary fungal infection. On the contrary, previous studies demonstrated a lower incidence of secondary bacterial and fungal infections, whereby Garcia-Vidal et al found an incidence of 3.8% and 0.7% of bacterial and fungal secondary infections, respectively.⁸ Additionally, the incidence of bacterial and fungal secondary infections was identified by Musuuza et al to be 20% and 8%, respectively.⁶

Our study had a predominance of gram-negative bacteria as the causative agent of secondary infection. Similarly, several studies observed an increased occurrence of gram-negative organisms as opposed to gram-positive.^{6,14,16–18} In line with Musuuza et al,⁶ the most prevalent pathogens in the current study were *P. aeruginosa* and *A. baumannii*. Secondary infection of the respiratory system was the most common followed by bloodstream infection. Our findings are consistent with a recently published cohort that reported pneumonia as the most frequent secondary infection followed by bacteremia in COVID-19 patients who were critically ill.¹⁷ This might be explained by the fact that patients necessitating ICU admission would likely require endotracheal intubation which predisposes them to hospital-acquired infections. The rise of fungal pathogens including *C. albicans* and *C. tropicalis* is of major concern. It is noteworthy that 75.9% of COVID-19 patients with secondary fungal infection have central venous catheters which increases the risk of *Candida* spp infection.¹⁹

Throughout the pandemic, multiple immunomodulatory therapies were proposed to target the host response to SARS-CoV-2, such as tocilizumab and corticosteroids.¹² However, the evidence on their possible side effects and involvement in the development of secondary infection remains scarce with heterogeneous findings. This study demonstrates a significant association between corticosteroids and secondary bacterial infections. Similarly, De Bruyn et al found a significant association between corticosteroids and secondary bacterial infection.¹⁷ Ritter et al, on the contrary, did not find an association between corticosteroids and secondary infections.²⁰ Although tocilizumab was not significantly associated with developing a secondary infection in the current study, the relationship between the two remains uncertain and arguable, requiring further research.^{7,12,21}

It is noteworthy that all patients in the present cohort have received antibiotics during their stay in the ICU. In comparison to the prescribing rate, a relatively lower incidence of coinfection and secondary infections was observed. Likewise, a multi-center prospective study found that 85.2% of the patients have received one or more antibiotics during their stay in spite of the low incidence of secondary and co-infections. In addition, it was observed that COVID-19 patients requiring ICU admission have received more antibiotics compared to those hospitalized in the ward.²² Though recommendations on the use of empirical antibiotic in severe disease varied between COVID-19 guidelines,^{23–25} a high-level of adherence to the principles of antimicrobial stewardship is vital to prevent the emergence of antimicrobial resistance bacteria, an infection with which is known to be associated with increased morbidity and mortality.^{24,26}

Similar to our results, a significant association between invasive mechanical ventilation and secondary infection was found by Costa et al. In addition, the duration of invasive mechanical ventilation was significantly associated with the development of secondary infection. The previous study reported a median duration of 24 days which is longer than what was observed in the present study.¹⁸ Congruent with our findings, Zhang et al reported a median duration of 4.5 days for developing a secondary infection following the initiation of invasive mechanical ventilation.¹³

Other factors were found to be associated with the development of secondary infection. The presence of comorbidities including hypertension, cardiovascular and renal diseases was found to be associated with secondary fungal infection. Diabetes mellitus, on the contrary, was not associated with bacterial nor fungal secondary infections, which opposes the findings of previous studies.^{12,17} It is noteworthy, however, that the present cohort is relatively small. Hence, it is plausible that factors potentially associated with developing secondary infection were undetected.

In line with previous studies,^{6,8,13,16,18} a higher mortality was observed in patients who suffered from secondary infection. A significant association was found between secondary bacterial infection and mortality, of which 65.7% deaths were reported. De Bruyn et al, in contrast, found an insignificant association between the risk of death and the development of secondary bacterial infection.¹⁷

In patients suffering from secondary infections, a longer ICU and hospital stay was observed, which is congruent with previous studies.^{8,17,18} Nevertheless, variations in the median length of stay were spotted in literature. In comparison to the current study, a longer stay was reported by Costa et al with a duration of ICU and hospital stays of 40 and 48 days, respectively.¹⁸ Garcia-Vidal et al, in contrast, reported a shorter stay of 5 and 20 days in the ICU and hospital, respectively.⁸ This variation could be attributed to multiple factors including the baseline health of the patients, the severity of their illness, the disparities between healthcare systems during COVID-19 crisis, and differences in mortality across studies. In addition, it remains uncertain whether secondary infections led to longer hospital stay or were a consequence of the latter. COVID-19 patients with secondary and co-infections might experience other complications including arrhythmia, shock, acute respiratory distress syndrome, and acute kidney injury. Complications as such may affect multiple systems in the body; consequently, leading to higher morbidity and mortality.²⁷

Conclusion

Bacterial and fungal secondary infections are common among COVID-19 patients in the ICU setting. The development of secondary infections was significantly associated with invasive mechanical ventilation. The most frequent pathogens identified in our study are *P. aeruginosa*, *A. baumannii*, and *C. albicans*. We recommend clinicians to consider these findings, along with other local studies, when selecting the proper empirical antibiotic therapy. Unfortunately, secondary infections predisposed patients to poor clinical outcomes, including higher mortality and longer hospital and ICU stays,

and have further increased the burden of this pandemic. Thus, it is imperative to reinforce the principles of infection control to ensure optimal outcomes and prevent undesired consequences.

Limitations and Recommendations

The main limitation of the present study lies in it being a single-center study with a small sample size, potentially limiting the generalizability of the findings. Thus, further larger scale multi-center studies are recommended. In addition, due to the retrospective design of the study, it is difficult to establish causation between different factors and the development of secondary infections. Therefore, future prospective studies are crucial to expand the knowledge on the predisposing factors associated with secondary infections among COVID-19 patients. Furthermore, the continuous change in the management guidelines since the discovery of the newly emerging virus might affect the outcome.

Disclosure

The authors report no conflicts of interest in this study.

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